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The Effects of Veratri Formosani Rhizoma on Some Central Actions of Paeoniae Radix

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ABSTRACT

In Chinese herb medicine, Paeoniae Radix(PR) and Veratri Formosani Rhizoma(VFR) are said to be incompatible and absolutely contraindicated to put them together in prescription. Both PR and VFR have their effects on the central nervous system. To elucidate why PR and VFR are incompatible in prescription, we used the anticonvulsive, sedative, analgesic and hypothermic effects as the indices to study the effects of VFR on the central actions of PR and found that VFR could antagonize the anticonvulsive, sedative, analgesic and hypothermic effects of PR.

INTRODUCTION

Traditional Chinese herb physicians often put different herbs together in their remedies. However, in the ancient Chinese medical book called Pentsao[1] (about 2000 years ago), 18 pairs of herbs were said to be absolutely incompatible and could not be put together at all. PR and VFR is one of the 18 pairs. Chinese herb physicians use PR in spasmodic abdominal pain[2] and VFR as a hypotensive or emetic[3-5]. Both herbs seem to act on the central nervous system[6-10]. In the present study, we investigated the effects of VFR on some central actions of PR to try to elucidate why these two herbs can not be administered concurrently.

MATERIALS AND METHODS

Preparations of test drugs

1000 gm of dried and smashed VFR or PR was immersed in 5000 ml of pure water at room temperature for one day and then extracted in water bath at a temperature just below 60°C several times until the solution was clear. The extracted solution was evaporated and concentrated by a rotary vacuum evaporator at a temperature around 55°C. The sample was obtained by lyophilizing the concentrated pulverizing it through a No. 80 # mesh.

Animals

Male ICR mice, weighing between 18-25 gm, were used in the studies of acute toxicity, anticonvulsive, sedative and analgesic effects. Male Sprague-Dawley rats, weighing between 190-230 gm were used in the study of hypothermic effect. The animals were maintained in groups of 5 per cage at a controlled temperature of 22±1°C and humidity of

55±5% and housed in a metal-wire cage for at least 7 days before each experiment. Solid diets (Sin-Lon Co., Taichung)and tap water were provided ad libitum.

Acute toxicity

A sufficient number of animals were used to obtain LD 50 (95% confidence limits) by the method of Litchfield and Wilcoxon[11].

Effects of VFR on the anticonvulsive effect of PR

PR(5g/kg, s.c.) was adiministered. 20 min later, pentylenetetrazol (120mg/kg, i.p.), strychnine nitrate (2mg/kg, i.p.), or picrotoxin (4mg/kg, i.v.) was administered. This group of mice was used as the positive control. In the negative control group, VFR (30mg/kg, i.p.) and PR (5g/kg, s.c.) was administered concurrently, 20 min later, pentylenetetrazol (120mg/kg, i.p.), strychnine nitrate (2mg/kg, i.p.), or picrotoxin (4mg/kg, i.v.) was administered. The latency to produce clonic and/or tonic convulsions and the time period between convulsions and death by gross observation were used as the indices of the effects of PR or PR/VFR on drug-induced convulsions.

Effects of VFR on the analgesic effect of PR

Hot plate method: In the positive control group, PR (2.5g/kg, s.c.) was administered. 20 min later, mice were placed on a hot plate[12](55±0.5°C). The latency to produce a pain response, jumping, licking or withdrawal legs was used as the index. In the negative control group, normal saline was administered. In the positive control group, VFR (30mg/kg, i.p) and PR (2.5g/kg, s.c) were administered concurrently.

Acetic acid method: In this experiment, 0.7%acetic acid (0.1ml/10g body weight) was administered intraperitoneally to producd pain. And the frequency of writhing response was used as the index of pain response.

Effect of VFR on the agonist sedative effect of PR

Hexobarbital (100 mg/kg, i.p.) was administered to produce sleep. And the sleep period was used as the index of sedative response. Normal saline, PR, and PR/VFR was used to see the effects on hexobarbital induced sleep.

Effects of VFR on the hypothermic effect of PR

In this experiment, only rats with a rectal temperature between 36.9-38.5°C were used. Normal saline, PR (2.5g/kg, 5g/kg, s.c.)or VFR(30mg/kg, i.p.)/PR (2.5g/kg, 5g/kg, s.c.) was administered. 20 min later, rectal temperatures were measured at intervals of one hour for 5 hours.

RESULTS

Acute toxicity

Table 1 shows the LD 50 and 95% confidence limits of PR(s.c.), VFR(i.p.)/PR(s.c.). VFR potentiated the acute toxicity of PR.

Effects of VFR on the anticonvulsive effect of PR

As shown in Table 2, PR prolongs the latencies of pentylenetetrazol and strychnine-induced convulsion ($p<0.05$). However, PR did not affect the latency of picrotoxin-induced convulsion. VFR/PR could shorten the latency prolonged by PR alone.

Effects of VFR on the analgesic effect of PR

As shown in Table 3 and 4, PR had significant analgesic effect. When VFR and PR were administered concurrently, the analgesic effect was decreased.

Effect of VFR on the agonist sedative effect of PR

As shown in Table 5, PR could shorten the latency of sleep induced by hexobarbital ($p<0.001$)and could prolong the duration of sleep induced by hexobarbital ($p<0.001$). VFR could antagonize the agonist sedative effect of PR.

Table 1. LD 50 and 95% Confidence Limits of VFR and PR in Mice

Drug	Route	LD50	95%confidence limits
VFR	I. P.	325mg/kg	276-382mg/kg
PR	P. O.	>15g/kg	
	I. P.	>10g/kg	
	S. C.	>10g/kg	
VFR+PR	I.P.+S.C.	112mg/kg	107.6-116mg/kg

Table 2. Effects of VFR on the Anticonvulsive Effect of PR

	Drug	C.C.(min)	T.D.(min)
Pentylenetetrazol (120mg/kg,i.p.)	Saline	0.80±0.08	4.01±0.44
	a)PR	1.09±0.08*	7.69±1.00**
	b)PR+VFR	1.11±0.07	4.38±0.64*
Strychnine (2mg/kg, i. p.)	Saline	0.98±0.08	1.75±0.17
	a)PR	1.43±0.18*	1.96±0.12
	b)PR+VFR	0.98±0.07	1.19±0.16**
Picrotoxin (4mg/kg, i. v.)	Saline	1.17±0.18	4.90±0.72
	a)PR	1.84±0.11	5.77±1.00
	b)PR+VFR	2.64±0.19	4.71±5.47

PR(5g/kg, s. c) and/or VFR(30mg/kg, i.p.) were given 20 min before injection of pentylenetetrazol, strychnine nitrate or picrotoxin. All results represent the mean±S. E. a)compared with control group, and b) Compared with PR group.*$p<0.05$,** $p<0.01$($n=10$).

Table 3. Effects of VFR on the Analgesic Effect of PR (Hot Plate Method)

Drug and dose	Reaction time(sec)		
	20min	40min	60min
Saline	13.12±2.68	4.75±0.75	6.00±0.91
PR 2.5 g/kg[a)]	10.58±0.99	8.46±0.34	8.41±0.52
PR 5.0 g/kg[a)]	13.75±1.39	10.75±0.92***	13.13±2.34*
PR 2.5 g/kg+VFR 30 mg/kg[b)]	9.52±0.92	8.11±0.33	7.60±0.55
PR 5.0 g/kg+VFR 30 mg/kg[b)]	10.75±2.27	8.69±1.65	7.63±1.51

PR(s.c.) and/or VFR(i.p.) were given 20 min before hot plate test. a)Compared with control group, and b) compared with PR group. All results represent the mean ±S.E. *$p<0.05$,***$p<0.001$($n=10$).

Table 4. Effects of VFR on the Analgesic Effect of PR (Acetic acid method)

Drug and dose	Writhing number	Protection(%)
Control	36.71±2.05	
PR 2.5 g/kg[a)]	20.71±2.86	43.58
PR 5.0 g/kg[a)]	15.00±5.69	59.14
PR 2.5 g/kg+VFR 30 mg/kg[b)]	23.42±2.03	36.18
PR 5.0 g/kg+VFR 30 mg/kg[b)]	20.56±5.72	43.99

Male mice were treated with PR(s.c.) and/or VFR(i.p.) 20 min before 0.7% aceic acid administration(i.p.), and number of writhing was counted for 10 min from 10 min after 0.7% acetic acid administration. a) Compared with control group, b)compared with PR group. Mean ±S.E.(n=10).

Table 5. Effects of VFR on the Agonist Sedative Effect of PR

Drug and dose	Onset (min)	Sleeping time (min)
Control	8.52±0.48	37.70±2.13
PR 2.5 g/kg[a)]	9.61±0.44	42.00±2.12
PR 5.0 g/kg[a)]	7.02±0.53***	48.30±1.56***
PR 2.5 g/kg+VFR 30 mg/kg[b)]	8.40±0.38	40.30±1.41
PR 5.0 g/kg+VFR 30 mg/kg[b)]	10.20±0.38	40.50±1.45**

Male mice were treated with PR (s.c.) and VFR (i.p.) 20 min before hexobarbital(100 mg/kg, i.p.) administration. a)Compared with control group, b)compared with PR group. Mean±S.E. ***$p<0.001$(n=10).

Table 6. Effects of VFR on the Hypothermic Effect of PR

Drug and dose	Time after administration(hr)				
	1	2	3	4	5
Control	37.81±0.15	37.74±0.11	37.81±0.11	37.74±0.05	37.58±0.13
PR 2.5 g/kg[a)]	37.30±0.27	37.20*±0.19	37.50±0.22	37.73±0.12	37.90±0.18
PR 5.0 g/kg[a)]	37.12*±0.28	37.22±0.25	37.40±0.15	37.90±0.18	37.98±0.20
VFR 30 mg/kg[a)]	36.72**±0.25	37.52±0.13	37.70±0.23	38.00±0.30	38.83±0.27
PR 2.5 g/kg+VFR 30 mg/kg[b)]	35.52***±0.36	35.55***±0.27	36.68±0.28	37.38±0.11	37.93±0.20
PR 5.0 g/kg+VFR 30 mg/kgb)	34.83***±0.15	35.57***±0.47	36.22±0.32	37.00±0.17	37.32±0.17

Male rats were treated with PR(s.c.) and/or VFR(i.p.) 20 min before taking rectal temperature. a)Compared with control group, b) compared with PR group. Mean±S. E.* $p<0.05$, **$p<0.01$, ***$p<0.001$(n=6).

Effect of VFR on the hypothermic effect of PR

As shown in Table 6, PR had hypothermic effect, VFR could increase the hypothermic effect of PR ($p<0.001$).

DISCUSSIONS

In the ancient Chinese medical book called Pentsao[1], PR and VFR were said to be incompatible and not to be used concurrently. To elucidate the mechanism of the incompatibility, the present study was performed. And we found that (1)VFR could increase the acute toxicity of PR, (2)VFR could decrease the anticonvulsive effect of PR, (3)VFR could decrease the analgesic effect of PR, (4)VFR could decrease the sedative effect of PR, and (5) VFR could increase the hypothermic effect of PR. The above facts imply that VFR could increase the toxicity and decrease the effectiveness of PR. These reasons may explain why PR and VFR should not be prescribed concurrently.

From these studies,we could also deduce the following facts:(1)PR cold potentiate hexobarbital-induced sleep. This fact implied that PR had a sedative effect. (2)Pentylenetetrazol and picrotoxin-induced convulsions were significantly inhibited by PR but strychnine-induced convulsions was not inhibited by PR. These facts implied that PR had anticonvulsive effect but its actions might not be at the spinal cord. Whether PR might be useful in patients with epilepsy deserves further study.

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中 文 摘 要

臺灣藜蘆對於芍藥之中樞神經系統作用之影響

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藜蘆與芍藥爲中藥十八反配伍禁忌之一，本研究係以芍藥之抗痙攣、鎮痛、鎮靜及降體溫等作用作爲實驗反應判定之指標，以探討中藥配伍禁忌之意義。實驗結果顯示臺灣藜蘆能拮抗芍藥之抗痙攣、鎮靜、鎮痛、並加強其降溫作用，顯見臺灣藜蘆與芍藥併用時，對於中樞神經系統有其相互之作用。本研究進一步證實古本草將藜蘆與芍藥列於十八反之內，當有其特殊之意義。